# A Review of Salvage Treatment Options for Disease Progression After Radiation Therapy for Localized Prostate Cancer

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## Abstract:

Recurrence of prostate cancer after initial treatment with radiation therapy is highly dependent on pre-treatment risk group and unfortunately, a proportion of patients fail primary treatment. The treatment of recurrence after primary radiation is rapidly changing with advances in imaging and it is important to distinguish those with a local failure from those with distant failure. If disease remains locally confined, salvage treatment with a variety of techniques can still provide a potential cure. Patients with distant failure are often treated with androgen deprivation, or in those with a shorter life expectancy, conservative management. In patients with a higher burden of metastatic disease, there is emerging evidence that chemotherapy and advanced androgen therapy can improve survival. We review the relevant literature on available salvage treatment options and appropriate patient selection for patients with recurrent prostate cancer after radiation therapy. We report on the efficacy and adverse effects of the currently available local salvage modalities including salvage radical prostatectomy, high dose rate and low dose rate brachytherapy, cryotherapy, high intensity focused ultrasound, and stereotactic body radiation therapy. We additionally discuss diagnosis of oligometastatic disease on imaging and current approaches to treatment with either radiation or surgery. While a full review of chemotherapy and advanced androgen therapies is beyond the scope of this article we briefly discuss their use in the treatment of newly diagnosed recurrence after radiation.

# 1. Introduction

Prostate cancer is the most commonly diagnosed non-dermatologic cancer in men in developed countries and has the second highest incidence to lung cancer among males globally.[1] Definitive treatment of disease confined to the prostate most commonly involves surgery, radiation therapy (RT) or a combination of both and patients over the age of 65 are more likely to receive radiation therapy than surgery.[2,3]

Failure of primary treatment is separated into biochemical failure and clinical failure. Biochemical failure relates to rising serum PSA after treatment, and is used to predict future clinical failure. Clinical failure is when a patient presents with symptoms related to local progression or distant metastasis of prostate cancer after treatment. Failure after primary radiation therapy is heavily influenced by pre-treatment risk grouping, but Nguyen et al. report that between 20% and 50% of patients may experience biochemical failure.[4] Rising PSA often predates clinical metastatic disease by many years and a subset of those with biochemical failure may continue to have organ-confined disease and benefit from additional local treatment.[5] Most patients with biochemical failure are managed with observation or androgen deprivation therapy (ADT) with only  a small minority receiving local salvage therapy, though local salvage therapy may be underutilized.[6]

In this review we will discuss which patients may benefit from local salvage therapy after failure of primary radiation therapy, and the general management of biochemical failure after primary radiation therapy. We will explore the various salvage treatment modalities and compare survival and morbidity outcomes.

# 2. Patient selection

Failure after primary treatment is most often diagnosed as biochemical recurrence (BCR) due to rising serum PSA. BCR after radiation therapy is defined as a rise of ≥2 ng/mL above post-treatment nadir PSA

value (Phoenix Definition)[7]. While recurrence is defined based on change in PSA, the absolute PSA value is associated with likelihood of recurrence and is predictive of time to metastatic disease[8,9]. Additionally, the absolute PSA at the time of salvage therapy is associated with biochemical failure free survival[10].

Among patients with biochemical recurrence in whom the site of recurrence is detected, disease isolated locally in the prostate gland and seminal vesicle is most common. According to a study of patients with clinically detectable recurrence at Memorial Sloan Kettering Cancer Center, the anatomic distribution of recurrence was 41.6% local, 9.7% lymphotropic, 20.3% osteotropic, and 28.5% multiorgan/visceral[11].

Patients with metastatic disease, or distant failure, are not often candidates for curative intent local salvage therapy, and it is therefore of particular importance to attempt to identify these patients to spare them the morbidity of a salvage treatment from which they may not benefit. The standard metastatic workup after biochemical failure has been a bone scan and cross-sectional imaging of pelvis for decades. However, advances in technology including positron-emission tomography (PET) with $^{18}$F-fluciclovine, choline C-11, or $^{18}$F sodium fluoride along with whole body MRI or CT have allowed for earlier detection of metastatic disease, and detection of small volume loco/regional disease recurrence.[12,13] Imaging using radio-labelled prostate specific membrane antigen (PSMA) is an additional promising new technology to help identify disease[14,15]. Despite these more sensitive tests, many patients who undergo local salvage treatment will develop distant failure, some of whom presumably had undetectable micrometastasis at the time of salvage and would have benefited from more restrictive patient selection. Patients with higher T stage and Gleason score at diagnosis as well as PSA doubling time (PSA-DT) after recurrence of less than 6 months are more likely to develop distant metastasis after attempted local salvage and may not benefit from local treatment.[16]

The recent advances in imaging have also allowed for identification of “oligometastasis” which describes the state of having limited metastatic spread, often to a single lymph node or distant locus. Patients with oligometastases may still be considered candidates for curative treatment and benefit from focal therapy to the identified lesion(s).

Patients with overt metastatic disease will not benefit from local salvage therapy, but in patients without evidence of metastasis the benefit of local salvage compared to ADT or observation is a controversial topic. Conclusions are based largely on small retrospective studies. The NCCN suggests that candidates for local salvage therapy are patients with original clinical stage T1-T2, Nx or N0, with life expectancy greater than 10 years, pre-salvage serum PSA <10 ng/mL, no evidence of distant metastasis based on imaging and PSA-DT, and a positive prostate biopsy.[17] None of the studies discussed in this article included only those patients meeting all of these criteria and it is therefore important to note the differing inclusion criteria for each study (Table 1).

# 3. Local salvage modalities

In patients who have radiographic and/or biopsy proven disease confined to the prostate after initial treatment with radiation therapy, local salvage treatment provides the possibility of a cure. However, only a small proportion of patients who fail primary radiation therapy receive local salvage treatment and there is currently no consensus on a best salvage treatment modality.[6] In evaluating local salvage options it is important to note that there are different definitions of biochemical failure, significant disparity in patient characteristics, and variation in the use of prior, neoadjuvant, and adjuvant ADT across the literature on this subject (Table 1).

## 3.1 Radical Prostatectomy

Salvage radical prostatectomy (SRP) after external beam radiation therapy (EBRT) is more technically difficult and is associated with higher potential for morbidity than primary radical prostatectomy (RP) due to effects of primary radiation on normal tissues in the pelvis. For these reasons SRP should be performed by an experienced physician at a high volume center and patients should also be counselled regarding the increased risk of side effects with this procedure. Removal of the prostate gland is achieved by open approach or minimally invasive robotic or laparoscopic technique. Nerve sparing techniques attempt to

preserve erectile function by leaving the neurovascular bundles intact but are only appropriate when tumor control will not be compromised. Pelvic lymph node dissection is often performed at the discretion of the surgeon and may be especially appropriate in the setting of oligometastatic disease confined to pelvic lymph nodes.

**Oncologic Outcomes**

In a multi-institutional, international case series, Chade et al. reported on the treatment of 404 patient with SRP after initial RT. The median age was 65 years and median pre-salvage PSA was 4.5 ng/mL. At a median follow up of 4.4 years they reported 5 year biochemical failure free survival (bFFS) of 48%, metastasis free survival (MFS) of 83% and cancer specific survival (CSS) of 92%.[18] These figures are similar to those reported by two smaller single center studies. Mandel et al. reported 5 year bFFS of 48.7% and CSS of 88.7% while Sanderson et al. reported progression free survival (PFS), which they define as time to ADT initiation or progression, of 47% at 5 years.[19,20] In a case series of 199 patients treated at the Naval Medical Center, bFFS was 58% and 48% at 5 and 10 years respectively.[21] Despite their slightly higher bFFS, they found a slightly lower CSS of 79% and 65% at 5 and 10 years respectively.

Taken as a whole, the literature for SRP suggest that in carefully selected patients with residual disease in the prostate, approximately half can be cured with surgery. However, it is important to note that patient selection for salvage is crucial, and most of the published series of SRP span many decades in which time radiation, surgical and imaging techniques have changed significantly.

**Adverse Effects**

As previously mentioned the morbidity of SRP can be significant. Ward et al. reported on morbidity after SRP, noting that 4% of SRP patients suffered operative rectal injury which increased to 10% of the patients who had undergone cystoprostatectomy due to radiation induced adhesions involving the rectal wall, bladder base, or trigone.[21] In a series of patient surveys from 33 patients at a median of 7.5 years

from SRP, Sanderson et al. reported that 73% of respondents found their overall urinary function to be "small," "very small," or "no" problem, while continence rates were higher among those who had received an artificial urethral sphincter.[20] Not surprisingly, they found a clinically significant improvement in sexual function in patients with inflatable penile prosthetic implant over patients with nerve sparing SRP, but found no difference in sexual bother between the groups. Bladder neck contractures were a common complication in both studies, occurring in 22%-41% of patients.[20,21]

## 3.2 Brachytherapy

In patients who have previously received EBRT, brachytherapy (BT) can be an appealing option due to the ability to deliver a very conformal high dose to the target lesion while minimizing dose to surrounding healthy tissue. There is also the convenience of as few as a single treatment session. The published literature for salvage brachytherapy includes a patient population that was largely treated with ADT prior to salvage brachytherapy, and variable rates of neoadjuvant ADT between study populations results in a wide range of biochemical control outcomes. However, in more contemporary and less pre-treated populations, low dose rate or high dose rate brachytherapy appear to be able to cure about half of all local failures in patients who are candidates for the procedures.

### 3.2.1 Low Dose Rate Brachytherapy

Low dose rate brachytherapy (LDR BT) is performed by implanting radioactive seeds directly into and around the target lesion or the entire prostate gland. Seeds remain in the gland permanently and deliver dose slowly over many months as the isotopes decay. Frequently used radioisotopes include $^{125}$I (half-life 59.4 days) and $^{103}$Pd (half-life 17.0 days).

**Oncologic Outcomes**

The largest reported case series of patients receiving salvage BT was published by Vargas et al. In this study of 69 patients, 89% of the patients received ADT neoadjuvantly and or adjuvantly and if patients

demonstrated serum PSA > 5 ng/mL while on ADT their cancer was considered castration resistant. Their 5-year bFFS was 73% for castration sensitive and 20% for castration resistant cancers. MFS and overall survival (OS) were 90% and 64% at 5 years.[22] In a study of largely high risk patients, Baumann et al. report on reduced dose brachytherapy with concurrent ADT and found relapse free survival to be 79% and 67% at 5 and 7 years respectively and distance metastasis free survival was 93% and 86% at 5 and 7 years[23]. Grado et al. reported on a series of 49 patients with median age 73.3 and pre-salvage PSA 5.6 excluding patients with neoadjuvant ADT or prior orchiectomy. With median follow up of 5.3 years they report 5-year bFFS, CSS, and OS of 34%, 79%, and 56% respectively.[24] Of these 49 patients, 11 had already failed one additional salvage modality and 2 had failed two previous modalities. More recently, Burri et al. reported on 37 patients at Mount Sinai with median age of 70 years and pre-salvage PSA of 5.6 ng/mL. They reported a bFFS of 54%, CSS of 96% and OS of 74% at 10 years.[25]

**Adverse Effects**

In a phase II prospective study of 92 patients previously treated with EBRT, Crook et al. found that LDR BT was well tolerated, with only 14% of patients experiencing late grade 3 GI or GU adverse events and no reported early or late grade 4 or higher events[26]. Moman et al. reported the toxicity experienced by 31 patients at 9 years median follow up and they found that 87% of their patients experienced grade 1-2 GU toxicity in the early phase within 90 days of treatment which decreased to 55% after 90 days.[27] The prevalence of grade 3 GU toxicity increased from 3% to 19% from the early to the late phase. Grade 1-2 GI toxicity occurred in 55% and 51% of patients in the early and late phase respectively. Grade 3 GI toxicity was rare and occurred in only 6% of patients in the late phase and no patients experienced grade ≥ 4 GI or GU toxicity. Grado et al. reported toxicities among their 49 patients which included two cases of persistent gross hematuria, three patients with significant penile dysuria, and two patients with rectal ulcers.[24] They found that acute urinary symptoms were common but typically transitory.

### 3.2.2 High Dose Rate Brachytherapy

Administration of high dose rate brachytherapy (HDR BT) involves insertion of catheters into the prostate guided by a perineal template. Highly radioactive isotopes such as $^{192}$Ir are inserted and moved through the catheters to distribute dose per the treatment plan. In some cases, patients may have the catheters implanted more than once and often multiple doses are delivered hours apart with a single implant.

**Oncologic Outcomes**

Chen et al. published a retrospective series of 52 patients undergoing salvage HDR BT with 36 Gy in 6 fractions across 2 separate implants. Patients had a median age of 67.5 and median pre-salvage PSA of 5.0 ng/mL. With median follow up of 59.6 months they found 5-year bFFS of 51% with OS of 92%.[28] In a prospective phase II study of HDR BT in 42 patients treated with 32 Gy in 4 fractions using a single implant, Yamada et al. reported a 5 year bFFS of 68.5% and OS of 79%.[29] This study excluded patients with pre-salvage PSA > 10 ng/mL and any patient with international prostate symptom score greater than 15.

**Adverse Effects**

Yamada et al. additionally evaluated treatment toxicity in their 42 patients.[29] They found acute grade 1-2 GU toxicity in 78% of patients, and up to 96% of patients in the late phase. There were 3 total grade 3 GU toxicity events with no grade 4 or greater. GI toxicity was largely transient rectal bleeding without any grade 3 or greater events. Chen et al. reported grade ≥2 acute and late GI toxicity in 38% and 56% of patients respectively with only 4% of patients experiencing any grade 2 GI toxicity.[28] Acute sexual dysfunction was found to be grade ≥2 in 19% of patients, increasing to 35% of patients for late dysfunction.

## 3.3 Cryotherapy

Cryotherapy, also known as cryosurgery and cryoablation therapy, involves placement of probes within the prostate that undergo extreme cooling using argon gas. Prostate tissue is consumed by an expanding

ball of ice that is monitored by transrectal ultrasound often through multiple freeze-thaw cycles.[30] Rapid freezing of the tissue results in ice crystal formation that leads to cell death.[31] A urethral warming catheter is used to prevent urethral tissue damage.

**Oncologic Outcomes**

Wenske et al. published a series of 328 patients who received salvage cryotherapy between 1994 and 2011 at Columbia University and had mostly received EBRT as primary treatment (49 patients had primary LDR BT and 20 patients had primary cryotherapy).[32] The median age was 65.8 years and median pre-salvage PSA was 4.0 ng/mL in the study. Their bFFS was 63% and 35% at 5 and 10 years respectively. CSS was 91% and 79% and OS was 74% and 45% at 5 and 10 years respectively. Lu et al. reported their series of 187 patients with mean follow up of 7.5 years and found disease free survival (DFS), which included results of serum PSA and some patients who received biopsies, to be 47% at 5 years and 39% at 10 years while MFS and OS were 87% and 95% respectively at 5 years.[33]

**Adverse Effects**

Long term complications of salvage cryotherapy were assessed with a survey of 112 patients at a median age of 68.8 years and mean follow up of 16.7 months.[30,34] They found that 72% of patients reported incontinence, 66% reported medium to severe voiding symptoms, 63% lost potency among those who were potent prior to cryotherapy, and 44% reported chronic perineal pain.[34] They additionally found a 33% overall satisfaction rate with cryotherapy. A similar report by Ng et al. fund that among 187 patients treated with salvage cryotherapy 8% required surgery to address complications after treatment.[35]

## 3.4 High Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU) is used in the treatment of localized prostate cancer through the ablation of tissue by heat generated by a beam of focused ultrasound using a transrectal probe.[36] The US Food and Drug Administration (FDA) approved HIFU to be marketed for use in prostate tissue ablation

only as recently as 2015 due to lack of substantial clinical outcome data.[37] There is limited data on HIFU outcomes relevant to patient decision making for primary treatment of prostate cancer and with this lack of primary treatment data, it follows that evidence in the context of local salvage therapy is even more sparse.

**Oncologic Outcomes**

Crouzet et al. published the largest series of 418 patients undergoing S-HIFU from 1995-2009 in an international, multi-institutional analysis.[38] Mean patient age was 68.6 years, on average 5.1 years after primary treatment. Mean pre-salvage PSA was 6.8 ng/mL and median follow up was 3.3 years. Some patients had a history of ADT use but none continued ADT after HIFU. Most patients received one HIFU session, with about 13% of patients receiving two or three sessions. They reported 37% of patients were free from initiation of ADT at 5 years but also report a bFFS of 49% overall at 5 years. Gelet et al. reported 30 month actuarial disease free rate (bFFS or negative biopsy) as 38% in their series of 71 patients with a median pre-salvage PSA of 5.7 ng/mL, and 13% of patients developed metastases.[39] Kanthabalan et al. reported a bFFS of 48% at 3 years with 92% overall survival among 150 patients.[40] Interestingly Uddin et al. biopsied a portion of their cohort of 84 patients treated with S-HIFU and found that 43% of those biopsied (25% of the entire cohort) demonstrated a positive biopsy after S-HIFU treatment.[41]

**Adverse Effects**

HIFU is less invasive than prostatectomy, but can still lead to significant morbidity. In an earlier study Crouzet et al. reported 16% of patients experienced bladder outlet obstruction. They also reported that 2% and 3% of patients developed a urethrorectal fistula and pubic bone osteitis respectively.[42] Gelet et al. found that 6% of their patients developed urethrorectal fistula.[39]

## 3.5 Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) is similar to EBRT except that the treatment dose is typically delivered in 2-5 total fractions. SBRT is an appealing non-invasive way to approximate the dosimetry achieved by HDR BT.[43] SBRT is a relatively new technique and there are few studies investigating the use of SBRT for local salvage therapy in prostate cancer.

Presenting preliminary results of their prospective study of 29 patients treated with salvage SBRT with 34 Gy in 5 fractions, Fuller et al. reported a bFFS of 82% at 2 years. The median age was 73 and median pre-salvage PSA was 3.1 ng/mL. They found GU toxicity of grade ≥2 in 18% of patients and no patients with GI toxicity above Grade 1. Of 10 patients who were sexually potent prior to SBRT, 4 reported no significant change while 3 experienced a major decrease in potency[44].

In another small series, Leroy et al. reported bFFS of 54% at two years among their 23 patients. Patients received 36 Gy in 6 fractions and had a median pre-salvage PSA of 2.5 ng/mL. They reported 26% of patients with GU toxicity grade ≥2 and two patients with grade 2 rectal toxicity.[45]

# 4. Treatment of Oligometastatic Disease

Treatment of oligometastatic disease typically consists of either radiation or surgery. Radiation therapy usually consists of SBRT while surgery involves salvage pelvic lymph node dissection (sPLND) when disease is confined to the pelvic nodes and metastasectomy for other isolated lesions. While there is growing interest and ongoing research investigating treatment of oligometastatic prostate cancer, published data remains sparse.

Ost et al. published a phase II trial comparing surveillance to metastasis-directed therapy (MDT) with either SBRT or surgery.[46] They found that the MDT group had a significantly longer median time to initiating ADT and no patients in the MDT group experienced grade 2 or greater toxicity. An Italian study of 40 patients evaluated the use of SBRT in patients with isolated lymph node recurrent prostate cancer.[47] They reported a two year bFFS of 44%.

Surgery for oligometastatic disease can target distant metastases, but most commonly will target lymphatic disease with salvage pelvic lymph node dissection (sLND). A German study of sLND investigated outcomes of surgery in patients with recurrent prostate cancer with lymphatic disease detected on imaging.[48] Most patients had received prostatectomy as primary treatment, but 10% of patients had received RT. Of the 69 patients included in the analysis, 27.3% demonstrated bFFS at 5 years and 35.1% remained free from systemic therapy at 5 years. Postoperative lymphocele occurred in 11.5% of patients, half of whom required surgical intervention. A study of 52 patients with recurrence after RP at Mayo Clinic found that sLND resulted in bFFS of 45.5%, MFS of 46.9%, and CSS of 92.5% all at 3 years.[49] This patient population was free from additional treatment in 46.2% of cases at last follow up. As with these studies, most evidence for sLND is in patients who underwent RP for primary treatment. Patients with recurrence after primary RT differ from RP patients in that they may have received previous radiation to their lymph nodes, and they retain their prostate gland. However, if imaging identifies disease isolated to the lymph nodes and surgical resection is feasible, it may be reasonable to assume similar outcomes in patients with recurrence after RT.

# 5. Systemic management options

In recent studies PET/CT is able to identify a lesion(s) in over 70% of patients with a PSA greater than 0.5.[14,15] However, advanced imaging is not always available, and even with advanced imaging some patients have only biochemical evidence of disease and are presumed to be metastatic. Patients with diffuse metastatic disease on imaging or other complicating factors may not be candidates for metastasis directed therapy, and for these reasons systemic treatment remains a common option for patients who fail radiation therapy.

## 5.1 Androgen Deprivation Therapy

Androgen deprivation therapy (ADT) is a staple in the treatment of metastatic prostate cancer and has additionally been associated with improved outcomes in localized disease.[50,51] Patients treated with ADT experience side effects including impotence, decreased libido, hot flashes, fatigue, and weight gain among others. There is evidence of an association with incident diabetes, coronary artery disease, myocardial infarction, and sudden cardiac death with ADT.[52]

The Timing of Androgen Deprivation (TOAD) trial was a randomized, non-blinded, phase III trial that included patients with biochemical recurrent disease without evidence of metastases (group 1) or who were not eligible for curative treatment (group 2) and evaluated the effect of immediate versus delayed initiation of ADT. Men assigned to the delayed arm were recommended to start ADT at least 2 years after randomization unless they developed symptoms, metastases, or a PSA doubling times of <6 months. This study found an improvement in OS in favor of immediate ADT, but among the group 1 patients this benefit did not reach statistical significance .[53] The immediate ADT group had more low-grade side effects, but overall quality of life was similar between the groups. Given the lack of an overall survival benefit for immediate initiation of ADT in patients with biochemical failure, many clinicians will delay initiation of ADT until an arbitrary cut off (e.g. PSA of 10) or until the PSA doubling time is <6 months.

### 5.1.1 Continuous vs Intermittent Androgen Deprivation Therapy

Traditionally, ADT was administered continuously beginning at the time of biochemical recurrence, but due to the significant side effects of ADT there has been interest in intermittent androgen deprivation (IAD). IAD allows for a treatment-free period, and in theory fewer side effects. In a randomized controlled non-inferiority trial of 1386 patients, Crook et al. compared IAD to continuous androgen deprivation. IAD was given in 8 month treatment cycles followed by non-treatment until PSA was >10. They found that OS was not inferior in the IAD group versus the CAD group.[54] The median survival was 8.8 vs 9.1 years in the IAD and CAD groups respectively. Their study additionally found symptom-based quality of life outcomes to favor IAD including hot flashes, desire for sexual activity, and urinary symptoms. In a randomized controlled trial of 1,535 patients with metastatic disease, Hussain et al.

similarly found fewer adverse events among the IAD group, however they were unable to conclusively demonstrate non-inferiority in regard to survival[55]. This study helps to support the paradigm of intermittent androgen deprivation, however it is difficult to directly apply the outcomes to our patient population since all of their patients had metastatic disease and a minority had been previously treated with radiation.

## 5.2 Chemotherapy

Recent studies have evaluated the efficacy of chemotherapy in patients with locally advanced and/or metastatic prostate cancer. The use of systemic therapy in the context of PSA-only recurrence without evidence of metastasis has been investigated, but these patients have made up a small portion of larger randomized trials.

The STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy) trial is evaluating various systemic therapies in local recurrent, locally advanced, and metastatic prostate cancer. The patient population being recruited into the STAMPEDE trial ranges from locally advanced (two high risk features) to metastatic, with the majority of patients having newly diagnosed metastatic disease without previous treatment.

In a publication evaluating the benefit of adding docetaxel, zoledronic acid, or both to standard of care (ADT +/- radiation) the STAMPEDE authors randomized 2,962 patients between 2005-2013.[56] Standard of care demonstrated a median overall survival of 71 months while addition of docetaxel resulted in a median overall survival of 81 months (HR 0.78; 95% CI 0.66-0.93; p=0.006). Addition of zoledronic acid to standard of care and to standard of care plus docetaxel did not demonstrate an advantage compared to standard of care plus docetaxel. Failure free survival favored the docetaxel group over standard of care alone (HR 0.61; 95% CI 0.53-0.70; p<0.001). However, the survival benefit in the setting of biochemical failure only is difficult to ascertain as only 6% of the patients in this study failed primary treatment. In

addition the survival benefit of chemotherapy came at the added cost of treatment toxicity with a 20% increase in grade 3-5 toxicity (32% vs 52%).

In a separate cohort of 1917 patients, the STAMPEDE authors investigated the effect of ADT alone versus ADT plus abiraterone and prednisolone. Failure free survival was 75% in the combination therapy group versus 45% in the ADT alone group (HR 0.29; 95% CI 0.25-0.34; p<0.001). Patients who received combination therapy experienced fewer symptomatic skeletal events than those who received ADT alone (HR 0.46; 95% CI 0.37-0.58; p<0.001), but again patients in the combination group were more likely to experience grade 3 or higher toxicity (47% vs 33%). [57] Again in this cohort only 5% of patients had been previously treated.

For patients with clinical or radiographic evidence of metastatic disease the CHAARTED trial randomized 790 patients with metastatic, hormone sensitive prostate cancer to receive ADT alone or ADT plus docetaxel.[58] There was an overall survival benefit with the addition of docetaxel over ADT alone (HR 0.61; 95% CI 0.47-0.80; p<0.001). Median time to castration resistant disease was 20.2 months for combined therapy compared to 11.7 months with ADT alone (HR 0.61; 95% CI 0.51-0.72; p<0.001). However, again the proportion of patients who had failed previous primary treatment was small (72.8% no prior treatment, 19.5% prostatectomy, and 7.6% radiation) making extrapolation to failure after primary RT difficult.

In a small phase II study of 41 patients, McKay et al. treated patients with docetaxel, bevacizumab, and ADT after biochemical recurrence following local therapy.[59] At 1 year after completion of therapy, only 44% remained free from biochemical recurrence and over half of their patients reinitiated ADT within two years due to disease progression. Additionally 39% and 12% of patients experienced grade 3 and grade 4 treatment-related adverse events and 22% of patients discontinued treatment due to toxicity.

Chemotherapy and advanced hormonal therapy are moving to the forefront of treatment for metastatic prostate cancer, but their role in treating patients after failure of primary radiation remains controversial.

Taken as a whole, the published randomized trials suggest that patients with a higher burden of disease (clinical or radiographic metastasis) are most likely to benefit from chemotherapy or advanced hormonal therapy after failure of primary radiation.

### 5.3 Watchful Waiting

In patients with recurrence who are elderly, have comorbid conditions, or otherwise elect to forego treatment, watchful waiting may be an appropriate strategy. In a retrospective study of men with PSA failure after radical prostatectomy the median time to development of clinical metastatic disease was 8 years from first biochemical failure, and the median time to prostate cancer specific death was 5 years from development of metastatic disease.[60] Clearly biochemical failure does not typically indicate imminent death from disease, and therefore in patients with a life expectancy <10 years aggressive salvage or hormonal treatment is unlikely to prevent clinical disease manifestation or death.

## 6. Conclusions

Salvage for failure after definitive RT for prostate cancer is a rapidly evolving field as newer imaging technologies are detecting more localized/oligometastatic disease. While there is no high quality comparative data to guide the decision of which local salvage therapy is best, it is reasonable to offer local salvage based on institutional strengths in patients with a pre-salvage PSA <10, life expectancy >10 years, PSA doubling time of >6 months, no evidence of distant disease, and either biopsy proven or imaging evidence of local failure. For patients with biochemical failure and no measurable disease, ADT remains the backbone of treatment, and this can be given continuously or intermittently with no difference in OS. Chemotherapy and advanced hormonal therapy have shown a survival benefit in patients with metastatic disease, but the benefit is likely greatest in those with a higher burden of disease.

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Table 1: Summary of studies evaluating salvage treatment options for prostate cancer

| Study | Study type | Patient Characteristics | Treatment | Oncologic Outcomes | Toxicity Outcomes |
|---|---|---|---|---|---|
| **Salvage Radical Prostatectomy (SRP)** | | | | | |
| Chade et al.[18]<br>2011<br>N=404 | Retrospective, international case series<br>1985-2009 | Median age 65<br>Median pre-salvage PSA 4.5 ng/mL<br>Median FU 4.4 yrs | SRP | bFFS: 48% at 5 yrs, 37% at 10 yrs<br>MFS: 83% at 5 yrs, 77% at 10 yrs<br>CSS: 92% at 5 yrs, 83% at 10 yrs<br>Pre-SRP PSA and gleason score at SRP predicted BCR and metastasis and positive LNs predicted metastasis | |
| Mandel et al.[19]<br>2016<br>N=55 | Single center, German case series<br>2007-2012 | Radiation OR HIFU recurrent disease<br>58.2% of patients met<br>Mean pre-salvage PSA 9.5 ng/mL<br>Median FU 3.0 yrs | SRP | bFFS: 48.7% at 5 yrs<br>MFS: 69% at 5 yrs<br>CSS: 88.7% at 5 years<br>Primary LDR BT and positive nodes correlated with worse bFFS<br>bFFS was 73.9% for patients within EAU guidelines vs 11.6% outside EAU guidelines | |
| Sanderson et al.[20]<br>2006<br>N=51, 33 with questionnaire | Single center retrospective case series + questionnaire<br>1983-2002 | Median Age 65<br>Median Pre-SRP PSA 8.0 ng/mL<br><br>Some patients received neoadjuvant ADT, post op ADT, orchiectomy.<br><br>Median FU 7.2 yrs | SRP | PFS: 47% at 5 yrs overall<br>Median OS was 12.9 yrs<br>PFS was 100%, 80% and 67% for patients with pT2N0, preop PSA </=5.0 or Gleason </=7 respectively at 5 yrs.<br>Pre-salvage PSA predictive of OS | QOL (median age 72 and median 7.5 years after surgery)<br>Total continence or occasional dribbling reported by 82% with and 69% without AUS device<br>Overall, 73% characterized overall urinary function as “small” “very small” or “no” problem.<br>Mean sexual function score was clinically significantly higher for inflatable penile prosthesis (IPP) patients while patients with nerve sparing technique did worse than IPP patients but better than standard SRP patients |
| Ward et al.[21]<br>2005<br>N=199 | Single Center, retrospective case series<br>1967-2000 | Life expectancy >/=10 years, all with positive prostate biopsy, no metastatic disease.<br>Median age: 65 years<br>Mean Preop PSA 8.5 ng/mL<br>Median FU 7.0 yrs | SRP or salvage cystoprostatectomy (SCP) | PFS: 67%, 58%, and 48% at 3, 5, and 10 years.<br>CSS: 87%, 79%, and 65% at 3, 5, and 10 years<br>Patients undergoing SRP did better than those requiring SCP: Median PFS of 8.7 vs 4.4 years.<br>Aneuploidy was strongest predictor of PFS<br>Pathological stage was strongest predictor of CSS | Intraop rectal injury in 4% of SRP and 10% SCP.<br>Complete continence maintained in 52%<br>Less overall morbidity in surgeries performed after 1990 as opposed to before |
| **Low Dose Rate Brachytherapy (LDR BT)** | | | | | |
| Crook et al.[26]<br>2019<br>N=92 | Prospective phase II study across 20 sites in the US and Canada<br>2007-2014 | Initial Tx: EBRT alone<br>Median age: 70 years<br>Positive biopsy >30 months after initial tx.<br>PSA <10 ng/mL<br>Gleason 7 (48%); all others Gleason 2-6<br>$^{99}$Tc bone scan and abdominal/pelvic CT showed no regional/distance disease<br>Median FU: 4.5 yrs | LDR BT<br>125-I 140 Gy or<br>103-Pd 120 Gy | | Late grade 3 treatment related GI/GU adverse events experienced by 14% of patients.<br>No late grade 4 or 5 events reported.<br>Only V100 (volume receiving 100% of the prescribed dose) was predictive of late GI/GU adverse events (OR 1.24; p=0.03).<br><br>Early grade 3 treatment related GI/GU adverse events experienced by 14% of patients.<br>No early grade 4 or 5 events reported.<br>Half of patients with early grade 3 adverse events developed late grade 3 adverse events. |

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| | | | | | The authors conclude that LDR BT after EBRT failure has acceptable tolerance. |
| Vargas et al.[22]<br>2014<br>N=69 | Single institution retrospective case series<br>1989-2011 | Initial Tx: EBRT alone<br>Average Age: 72.5 years<br>Positive biopsy more than 2 years after initial tx<br>PSA >5ng/mL while on HT were considered castration resistant prostate cancer (CRPC)<br>Androgen suppression was used in 89% of cases neoadj and adjuvantly<br><br>Median FU 5.0 yrs | LDR BT<br>103-Pd 100 Gy | bFFS: 73.8% in non-castration resistant disease vs 20% in castration resistant patients at 5 yrs<br>MFS: 90% at 5 yrs<br>OS: 64% at 5 yrs<br><br>Excluding CRPC patients (n=60) 5 year bFFS was 85.6%, 74.8%, and 66% for low, intermediate, and high risk patients respectively.<br><br>5 year bFFS was 77.7% and 43.3% without and with treatment delay as defined as receiving 6 months of ADT prior to salvage BT | |
| Grado et al.[24]<br>1999<br>N=49 | Mayo Clinic Scottsdale<br>retrospective case series<br>1990-1996 | Median age: 73.3<br>Initial tx: 46 EBRT, 3 BT<br>PreSalvage PSA: 5.6 ng/mL (not including patients with neoadj ADT or prior orchiectomy<br>11 patients had already failed additional modality and 2 had failed two additional modalities.<br>One patient had mets while 48 had no evidence of mets at time of salvage<br><br>Median FU 5.3 yrs | LDR BT (37 patients with Pd103 median 120 Gy and 12 with I125 median 160 Gy.)<br><br>4 received adjunctive radiation therapy and 8 received neoadj hormone therapy | bFFS: 48% at 3 yrs, 34% at 5 yrs<br>CSS: 89% at 5 yrs, 79% at 5 yrs<br>OS: 75% at 3 yrs, 56% at 5 yrs<br>Post-Salv PSA nadir of <0.5 ng/mL associated with improved bFFS (RR 4.25 for patients with 0.5 ng/mL or more) | Acute Complications: frequency, urgency, hesitancy, nocturia common during first 3 months but transient and managed with alpha-blocker<br>Sexual Side effects: Only 1 patient reported decreased capacity for sexual activity after salvBT but 60% of patients were not sexually active prior to salvage. |
| Burri et al. [25]<br>2010<br>N=37 | Mount Sinai single center retrospective case series<br>1994-2008 | Median age at salvage: 70<br>Median PSA at salvage: 5.6 ng/mL<br>Initial tx: 32 EBRT, 5 BT<br>Median FU 7.2 yrs | LDR BT (Pd103 110 Gy, I125 135Gy) | bFFS: 65% at 5 yrs, 54% at 10 yrs<br>LRFS: 84% at 5 yrs, 76% at 10 yrs<br>DMFS: 94% at 5 yrs, 79% at 10 yrs<br>CSS: 96% at 5 yrs, 96% at 10 yrs<br>OS: 94% at 5 yrs, 74% at 10 yrs | |
| Moman et al.[27]<br>2010<br>N=31 | Single center<br>Retrospective case series<br>1994-2009 | Initial Tx: 20 EBRT and 11 125-I<br><br>Mean age 69.3 years<br><br>Mean pre-Salv PSA 11.4 ng/mL<br>With mean doubling time of 13 months<br><br>Median FU 9.0 years | LDR BT<br>125-I 145 Gy | bFFS: 51% at 1 yr, 20% at 5 yrs<br>CSS: 74% at 5 yrs, 46% at 10 yrs<br>OS: 72% at 5 yrs, 39% at 10 yrs<br><br>Gleason >7 had HR 12.4 for BCR compared to Gleason ≤7 | GU Toxicity: 87% and 55% of patients had grade 1-2 toxicity in acute (<90 days) and late phase (>90 days) respectively. Grade 3 toxicity occurred in 19% in late phase<br><br>GI Toxicity: 55% and 51% of patients had grade 1-2 toxicity in acute and late phase respectively. Grade 3 toxicity occurred in 6% in late phase. |
| Baumann et al.[23]<br>2017<br>N=33 | US retrospective case series<br>1998-2013 | Initial Tx: EBRT<br>Median age: 75 years<br>Median pre-salvage PSA 5.0 ng/mL<br>High risk disease in 55% of patients<br>Median FU: 5.1 yrs | LDR BT 103-Pd 100 Gy (N=25) or HDR BT 30 Gy in 6 fractions (N=8)<br><br>All received 4-6 months neoadjuvant plus adjuvant ADT | Relapse free survival: 79% at 5 yrs, 67% at 7 yrs<br>DMFS: 93% at 5 yrs, 86% at 7 yrs<br>OS: 94% at 5 yrs, 85% at 7 yrs<br><br>Age at diagnosis, PSA nadir after EBRT, age at recurrence, and presalvage PSA were significant predictors of relapse free survival after salvage. | Late grade 3 GU toxicity occurred in 12% of patients with resolution or significant improvement 3 of 4 of these cases.<br><br>1 patient experienced late grade 1 GI toxicity but no other cases of GI toxicity were reported.<br><br>ADT resulted in grade 2 endocrine toxicity in 30% of patients. |
| High Dose Rate Brachytherapy (HDR BT) | | | | | |
| Chen et al. [28]<br>2013<br>N=52 | Single institution retrospective case series<br>1998-2009 | 77% patients had increase in Gleason score at recurrence vs primary tx.<br><br>Median age: 67.5<br>Median PSA 5.0 ng/mL | HDR BT<br>36 Gy in 6 fractions in 2 separate implants performed 1 week apart | bFFS: 51% at 5 yrs<br>OS: 92% at 5 yrs<br><br>No significant predictors of biochemical control | GU Toxicity: 2% of patients had grade 3 toxicity. No grade 4 or 5.<br>GI: No grade 3 or higher acute or late GI toxicity. Late grade 2 GI in 4% |

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| | | Median FU 5.0 yrs | | | |
| Yamada et al.[29]<br>2014<br>N=42 | Prospective phase II study<br>2007-2011 | Biopsy proven recurrence after definitive EBRT<br><br>Median age: 72<br>Median presalv PSA: 3.5 ng/mL<br><br>18 patients had ADT presalvage but all discontinued after HDR BT<br><br>Excluded: any patient with PSA >10ng/mL at assignment and international prostate symptom score IPSS >15 before salvage therapy. Hx of inflammatory bowel disease, prior rectal surgery. Abnormal coag studies.<br><br>Median FU 3.0 yrs | HDR BT<br><br>192-Ir 32 Gy in 4 fractions in 1 implant | bFFS: 68.5% at 5 yrs<br>DMFS: 81.5% at 5 yrs<br>OS: 79% at 5 yrs | GU Toxicity: Acute Grade 1 and Grade 2: 38% and 40%. Late Grade 1 and Grade 2: 48% and 48%. 3 total Grade 3 events but no Grade 4 or greater.<br><br>GI: Late Grade 1 and Grade 2 GI toxicity 43% and 14% without Grade 3 or higher. Most GI complications consisted of transient rectal bleeding. |
| Salvage Cryotherapy (SC) | | | | | |
| Pisters et al.[30]<br>1997<br>N=150 | MD Anderson retrospective case series<br>1992-1995 | Median age 68.8 years<br>91% Caucasian<br>Initial Tx:<br>-Group 1: RT only (98 EBRT only, 4 LDR BT only, 8 EBRT and LDR BT.)<br>-Group 2: Combination of therapies (27 EBRT + HT, 6 EBRT + HT+CT, 1 EBRT + CT, 4 HT only, 2 HT + CT)<br>Mean FU 1.4 yrs | SC | bFFS: 42% overall<br><br>Among group 1 patients, BCR was more prevalent in patients who received only one freeze-thaw cycle compared to two. Also the negative biopsy rate after double freeze-thaw cycle was 93% compared to 71% for single cycle. | Urinary incontinence reported in 73%, obstructive symptoms in 67%, impotence in 72%, and severe perineal pain in 8%. |
| Wenske et al. [32]<br>2013<br>N=328 | Columbia University NYC retrospective case series<br>1994-2011 | Median Age 65.8 years<br>Median Presalv PSA 4.0 ng/mL<br>Median time to SC 67.5 mo after primary RT or cryosurgery<br>Initial tx: 259 EBRT, 49 LDR BT, 20 cryosurgery<br><br>Median FU 4.0 yrs | SC | bFFS: 63% at 5 yrs, 35% at 10 yrs<br>CSS: 91% at 5 yrs, 79% at 10 yrs<br>OS: 74% at 5 yrs, 45% at 10 yrs<br><br>PSA nadir after SC was predictive of bFFS and CSS. | Urethral stricture requiring intervention in 4.6%, bladder outlet obstruction requiring intervention in 3.4%. Rectourethral or urethroperineal fistula formation in 1.8%.<br><br>55 of the patients underwent focal SC of affected lobe. Overall Survival was better for this cohort but rectourethral fistula formation occurred in 5.5% |
| Williams et al.[33]<br>2011<br>N=176 of 187 | Canadian retrospective case series<br>1995-2004 | Median age: 70.9 years<br>Median presalvage PSA: 4.9 ng/mL<br>71% had neoadjuvant ADT for 3-6 months for downsizing<br>Initial tx: 183 EBRT, 3 BT, 1 EBRT+BT.<br>Mean FU 7.5 yrs | SC | DFS (recurrence including BCR): 47%, 39%, and 39% at 5, 8, 10 yrs<br>MFS: 87%, 83%, 82% at 5, 8, 10 yrs<br>OS: 95%, 91% and 87% and 5, 8, and 10 yrs<br><br>Post salvage nadir >1 had RR 6.63 for recurrence p<0.001<br>Presalvage PSA<5ng/mL had DFS 64% at 10 years as opposed to 6.7% with PSA>10 ng/mL<br>Pres-alvage Gleason and pre-intial tx PSA both also correlated with DFS | |
| Perrotte et al.[34]<br>1999<br>N=112 of 150 | MD Anderson cross sectional study of quality of life<br>1992-1999 | Median age 68.8 years<br>91% Caucasian<br>Initial Tx:<br>-Group 1: RT only (98 EBRT only, 4 LDR BT only, 8 EBRT and LDR BT.) | SC | | Incontinence: 72% report dribbling or leakage of urine<br><br>Voiding Symptoms: Medium to severe symptoms in 66% of patients. More cases of voiding symptoms without use of urethral warming catheter (93% vs 55% of patients) |

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| | | -Group 2: Combination of therapies (27 EBRT + HT, 6 EBRT + HT+CT, 1 EBRT + CT, 4 HT only, 2 HT + CT)<br><br>Mean FU 1.4 yrs | | | Sexual Function: 41% of patients were potent prior to SC down to 15% after tx. Double freeze-thaw cycle group had significantly worse potency after tx (8% vs 23%)<br><br>Pain: 44% report some degree of chronic perineal pain or discomfort. 70% vs 34% had pain with vs without urethral warming catheter.<br><br>33% overall satisfaction rate with SC |
| Ng et al.[35]<br>2007<br>N=187 | Canadian retrospective case series<br>1995-2004 | Median age: 70.9 years<br>Median presalvage PSA: 4.9 ng/mL<br>71% had neoadjuvant ADT for 3-6 months for downsizing<br>Initial tx: 183 EBRT, 3 BT, 1 EBRT+BT.<br>Mean FU 3.3 yrs | SC | bFFS: 56% in patients with pre-salvage PSA ≤4 ng/mL, 29% with PSA 4-9.99 ng/mL, and 14% with PSA ≥10 ng/mL at 5 yrs.<br>OS: 97% at 5 yrs, 92% at 8 yrs | 8% of patients needed additional surgery for complications |
| High Intensity Focused Ultrasound (HIFU) | | | | | |
| Crouzet et al.[38]<br>2017<br>N=418 | International retrospective case seriers<br>1995-2009 | Mean time between initial tx and salvage: 5.1 years<br>Mean age 68.6 years<br>Mean pre-salvage PSA 6.8 ng/mL<br>191 patients had hx of ADT but none continued after HIFU.<br>87.1% of patients had one session of HIFU while 12.2% and 0.7% had two and three session respectively<br>Median FU 3.3 yrs | HIFU | bFFS: 49% at 5 yrs overall. 58%, 51%, and 36% for pre-EBRT low, intermediate, and high risk patients or 67%, 42%, and 22%, for pre-S-HIFU PSA levels of ≤4, 4-10 and ≥10 ng/mL respectively.<br>MFS: 81% at 7 yrs<br>CSS: 82% at 7 yrs<br>OS: 72% at 7 yrs<br>Lower PSA nadir after S-HIFU correlated with decreased need for ADT after salvage. | |
| Gelet et al.[39]<br>2004<br>N=71 | Single center French retrospective case series<br>1995-2003 | No staging pre-HIFU<br>Median presalv PSA 5.7 ng/mL<br>Mean age 67<br><br>Mean 1.2 yrs | HIFU | DFS: 38% at 2.5 yrs<br>Negative biopsy rate of 73% at 2.5 yrs<br>Metastasis observed in 12.7% overall | 6% developed urethrorectal fistula |
| Kanthabalan et al. [40]<br>2017<br>N=150 | UK retrospective case series<br>2006-2015 | Mean age: 69.8 years<br>Mean pre-salvage PSA 5.5<br>45.3% with pre-salvage ADT<br>Median FU 2.9 yrs | HIFU | bFFS: 48% at 3 yrs overall. 100%, 61%, and 32% at 3 yrs for low intermediate and high risk groups.<br>OS: 92% at 5 yrs | |
| Ahmed et al.[41]<br>2012<br>N=84 | Two site international retrospective case series<br>2004-2009 | Mean age 68.3<br>Median Presalv PSA 3.8 ng/mL<br>Initial Tx: all EBRT<br>Gleason 6-7 only<br><br>Median FU 1.7 yrs | HIFU | PFS: 59% at 1 yr, 43% at 2 yrs<br>8% of patients did not respond to therapy and had increased PSA after therapy<br><br>25% of whole cohort and 43% of those biopsied had residual disease on biopsy following salvage HIFU | |
| Crouzet et al.[42]<br>2012<br>N=290 | French retrospective case series<br>1995-2009 | Mean age 68.7<br>Mean PSA 6.38 ng/mL<br>D'Amico risk group: 19% low risk, 31.4% intermediate, and 43% high risk and undefined in 6.6%<br>Mean time from Initial tx to salvage was 60 months<br>50% received ADT prior to salvage at some point | HIFU | PFS: 45%, 31%, and 21% at 5 yrs for low, intermediate, and high risk groups<br>MFS: 80% at 5 yrs, 79.5% at 7 yrs<br><br>Increased risk of progression with higher pre-salvage PSA, previous ADT, and Gleason ≥8 vs Gleason ≤6 | 6 cases of urethrorectal fistula, 8 cases of pubic bone osteitis. 16% experienced bladder outlet obstruction. |

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| | | Median FU 2.3 yrs for PFS and 4.0 yrs for CSS and MFS | | | |
| **Stereotactic Body Radiation Therapy (SBRT)** | | | | | |
| Fuller et al.[44]<br>2015<br>N=29 | Prospective single arm study<br>2009-2014 | At least 2 years since prior RT<br>Median age 73<br>Median presalv PSA 3.1 ng/mL<br>Median interval between initial tx and salvage 88 months<br>Initial tx: 27 EBRT, 1 BT, 1 SBRT<br>7 on ADT at time of initial failure but none received neoadj or adjuvant ADT<br><br>Median FU 2.0 yrs | SBRT<br>34 Gy in 5 fractions | bFFS: 82% at 2 yrs | GU Toxicity: 18% report ≥grade 2 with one case of grade 3 and one case of grade 4.<br><br>GI Toxicity: No acute or late GI toxicity greater than grade 1<br><br>Sexual function: Data available on 10 patients who were potent before salvage tx. Three patients had a major decrease in potency while four had no significant change. (SHIM scoring) |
| Leroy et al.[45]<br>2017<br>N=23 | Retrospective single institution case series<br>2011-2014 | Median age 70 yrs<br>Initial tx with EBRT or BT +/- ADT<br>Median pre-salvage PSA 2.5 ng/mL<br>Recurrence at least 2 yr after initial tx<br>Median FU 1.9 yrs | SBRT<br>36 Gy in 6 fractions | DFS: 54% at 2 yrs<br>OS: 100% at 2 yrs<br>LRFS: 76% at 2 yrs | Grade 3 toxicity in 9% of patients (cystitis and neuralgia)<br>Grade 1-2 urinary toxicity was common<br>No grade 4 or higher toxicity reported |
| **Oligometastatic Disease** | | | | | |
| Ost et al.[46]<br>2017<br>N=62 | Multicenter, randomized, phase II study<br>2012-2015 | Median age 64 (surveillance) and 62 (MDT) yrs<br>Median PSA at inclusion was 3.8 ng/mL for surveillance and 5.3 for MDT<br>One metastasis in 29% of surveillance group vs 58% of MDT group<br>Median FU 3 yrs | Metastasis directed therapy (MDT) with SBRT or surgery vs Surveillance for oligometastasis | Median ADT-free survival was 13 months for surveillance group and 21 months for MDT group.<br>Local progression in 6 of surveillance group versus none of the MDT group.<br>PSA decline observed in 35% for surveillance group versus 75% in MDT group. | Grade 1 toxicity in 17% of the MDT patients without grade 2 or higher events.<br><br>No difference in quality of life between the two groups |
| Ingrosso et al.[47]<br>2016<br>N=40 | Italian retrospective case series<br>2008-2014 | Median age 74 yrs<br>Median Gleason 7<br>Primary Tx was surgery, EBRT, or BT<br>Median PSA 4.2 ng/mL<br>Median FU 2.0 yrs | SBRT for oligometastasis | bFFS: 44% at 2 yrs<br>OS: 95% at last FU<br>1 patient with failure within the treatment field | Grade 2 toxicity in one case (acute phase diarrhea)<br><br>Grade 3 toxicity in one case (late phase dyspepsia) |
| Porres et al.[48]<br>2017<br>N=87 | German prospective study<br>2009-2016 | Mean age 66.7 yrs<br>Mean pre-salvage PSA 2.63 ng/mL<br>Primary Tx was RP in 87.4% +/- adjuvant or salvage RT. Primary tx of RT in 10.3% of patients.<br>Median FU 1.8 yrs | Salvage pelvic lymph node dissection (sLND) | Only 69 patients with complete follow up included in survival analysis<br>bFFS: 35.5% and 27.3% at 1 and 5 yrs<br>Systemic therapy-free survival: 63.4% and 35.1% at 1 and 5 yrs.<br>Number of positive lymph nodes and biochemical response 6 weeks after surgery were identified as predictors of bFFS and ADT-free survival. | One intraoperative obturator nerve lesion<br><br>Postoperative lymphocele occurred in 11.5% of cases, half of which required surgical intervention. Two patients with obstructive ileus also required surgery. |
| Karnes et al. [49]<br>2015<br>N=52 | Mayo Clinic retrospective case series 2009-2013 | Median age 60 yrs<br>Median pre-salvage PSA 2.2 ng/mL<br>Primary Tx was RP in all cases<br>Other therapy after RP in 78.8% of cases before sLND<br>Median FU 1.7 yrs | Salvage pelvic lymph node dissection (sLND)<br><br>82.7% received adjuvant hormone therapy | bFFS: 45.5% at 3 yrs<br>MFS: 46.9% at 3 yrs<br>CSS: 92.5% at 3 yrs<br><br>No further treatment after sLND in 46.2% of patients at last follow up. | |
| **Androgen Deprivation Therapy (ADT)** | | | | | |
| Duchesne et al.[53]<br>2016<br>N=261 | Randomized Phase 3 trial<br>2004-2012 | Group 1: patients with PSA relapse after tx. No more than 12m adj or neoadj ADT and ADT must have been completed at least 12 m prior to randomization. | Immediate vs delayed ADT<br><br>Immediate: received tx within 8 | Combined: 5 year OS 86.4% in delayed vs 91.2% in immediate. Trend toward increased survival in immediate with unadjusted HR of 0.55 (95% CI 0.30-1.00; p=0.050)<br><br>Group 1 results: | Delayed arm demonstrated fewer treatment associated adverse events than immediate arm.<br><br>Did not demonstrate relevant difference in quality of life between arms |

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| | | Group 2: Asymptomatic men unsuitable for curative tx because of age, comorbidity, or locally advanced disease.<br><br>Excluded if PSA- doubling time <,3 months<br><br>Median FU 5.0 yrs | weeks of randomization<br><br>Delayed: Treatment was not to begin until at least 2 years after randomization unless symptoms or mets developed, or PSA doubling time decreased to <6m. | 5 year OS 78.2% vs 84.3% for delayed vs immediate tx respectively. The adjusted HR for death was 0.54 in favor of immediate tx but not statistically significant (p=0.074).<br><br>Statistically significant difference in local progression that favored immediate tx but this was not observed with distant progression.<br><br>41% of men in delayed arm did not reach a trigger (in other words they made it the full 2 years before starting ADT) | |
| Crook et al.[54]<br>2012<br>N=1,386 | Randomized controlled trial<br>1999-2005 | Definitive RT >12 m before enrollment<br>PSA >3 ng/mL and higher than post-RT nadir<br>No evidence of mets<br>Serum testosterone >5 nmol/L<br>Life expectance >5 y<br><br>Median FU 6.9 yrs | Intermittent androgen deprivation (IAD) vs continuous androgen deprivation (CAD)<br><br>IAD: 8 months of treatment followed by surveillance until PSA above 10 ng/mL | Median overall survival was 8.8 years in intermittent-therapy group and 9.1 years in the continuous-therapy group.<br><br>HR for death with IAD vs CAD was 1.02 (95% CI, 0.86 to 1.21) which met noninferiority criteria (HR <1.25) with a p-value of 0.009<br><br>Significant improved outcomes across groups: age <75 yr, >3 yr since RT, baseline PSA 3-15 ng/mL, and no prior HT. | QOL:<br>-Functional domains non-significant trend in favor of IAD<br>-Symptoms: Hot flashes, desire for sexual activity, and urinary symptoms all significantly better with IAD (p<0.05) in addition to a trend toward improved fatigue (p=0.07).<br><br>Potency on IAD: only 29% of those potent at baseline recovered potency during non-treatment interval. |
| Hussain et al.[55]<br>2013<br>N=1,535 | Randomized controlled trial<br>1995-2008 | Prior radiation therapy in 29% and prior radical prostatectomy in about 20% of patients.<br>All patients had metastatic disease<br>Median age 70 yrs<br>Median pre-ADT PSA: 42 ng/mL<br>Patients were randomized after showing response to ADT | Intermittent androgen deprivation (IAD) vs continuous androgen deprivation (CAD)<br><br>Patients received luteinizing hormone-releasing hormone agonist and anti-androgen agent. | They could not demonstrate statistically significant inferiority or non-inferiority of IAD compared to CAD. The IAD group experienced more deaths with HR 1.10 but 90% CI (0.99, 1.23). Median survival after enrollment was 5.7 yrs for IAD vs 6.4 yrs for CAD | IAD was associated with better quality of life related to impotence (p<0.001), libido (p=0.04), and mental health (p=0.003)<br><br>At 15 months, 78% of the IAD group had resumed hormone therapy. |
| Chemotherapy | | | | | |
| James et al. [56]<br>2016<br>N=2962 | RCT<br>2005-2013 | Median age 65 yrs<br>Prior local therapy in 6% of patients.<br>M+ disease in 61%, N+/X M0 in 15%, N0M0 in 24%.<br>Median FU 3.6 yrs | Four groups: Standard of care (SOC) only (HT), SOC +zoledronic acid (ZA), SOC + docetaxel (Doc), and SOC + ZA +Doc | Survival advantage identified for SOC + Doc (HR 0.78, 95% CI 0.66-0.93; p=0.006) and SOC + ZA + Doc (HR 0.82, 95% CI 0.69-0.97; p=0.022) groups versus the SOC alone group<br><br>Failure free survival advantage for SOC + Doc (HR 0.61, 95% CI 0.53-0.70; p=$0.413x10^{-13}$) and SOC + ZA + Doc (HR 0.62, 95% CI 0.54-0.70; $0.134x10^{-12}$) | Grade 3-5 toxicity occurred in 52% of patients in both the SOC + Doc and SOC + ZA + Doc groups overall.<br><br>At 6 months after treatment, Grade 3-5 toxicity occurred in 17% for SOC only, 15% for SOC + ZA, 36% for SOC + Doc, and 39% for SOC + ZA + Doc |
| James et al.[57]<br>2017<br>N=1917 | RCT<br>2011-2014 | Median age 67 yrs<br>Median PSA 53 ng/mL<br>Median FU 3.3 yrs<br>Additional RT in 41%<br>Included patients who were newly diagnosed and metastatic, high risk locally advanced, or relapsed after primary surgery or RT. | ADT alone vs combination therapy (ADT plus abiraterone acetate and prednisolone) | Failure free survival: 75% in combination therapy group vs 45% in ADT alone group (HR 0.29; 95% CI, 0.25 to 0.34; p<0.001) at 3 yrs<br>CSS: 76% in combination group vs 82% in ADT alone group overall | Any grade 3 or higher adverse event in 47% of combination group vs 33% of ADT alone group.<br><br>Grade 5: 12 events in combination group vs 3 events in the ADT along group. |
| Sweeney et al.[58]<br>2015 | RCT<br>2006-2012 | Median age 64 yrs in ADT + Doc group and 63 yrs in ADT alone group | ADT alone vs ADT + Docetaxel (Doc) | Overall survival benefit for ADT + Doc group over ADT alone (HR 0.61; 95% CI 0.47-0.80; p<0.001) | Grade 3 toxicity occurred in 16.7% of patients.<br>Grade 4 toxicity occurred in 12.6% of patients. |

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| N=790 | | Median PSA at start of ADT was 50.9 in ADT + Doc group and 52.1 in ADT alone group<br>No local therapy in 72.8% in both groups. Primary tx of RT or RP in others<br>Median FU 2.4 yrs | | Decrease in PSA level to <0.2 ng/mL occurred in 27.7% in the ADT + Doc group and 16.8% in ADT alone group (p<0.001).<br><br>Median time to castration resistant disease was 20.2 months for ADT + Doc group vs 11.7 months for ADT alone (HR 0.61; 95% CI 0.51-0.72; p<0.001) | One patient experienced grade 5 toxicity event (sudden death).<br><br>Most common grade 3-4 events were fatigue, neutropenia, and febrile neutropenia. |
| McKay et al. [59]<br>2015<br>N=41 | Single arm phase 2 study<br>2008-2010 | Median age 58-60 yrs<br>Previous tx included RP in 36, 29 of whom received salvage RT. The other 5 patients had primary RT.<br>Median FU 2.3 yrs | Docetaxel, bevacizumab, dexamethasone, and ADT | 80% developed PSA progression with median time to progression of 27.5 months | Grade 3 treatment related adverse events in 39%<br><br>Grade 4 treatment related adverse events in 12% |

Acronym definitions:

Salvage radical prostatectomy (SRP); external beam radiation therapy (EBRT); low dose rate brachytherapy (LDR BT); high dose rate brachytherapy (HDR BT); salvage cryotherapy (SC); high intensity focused ultrasound (HIFU); stereotactic body radiation therapy (SBRT); biochemical recurrence (BCR); biochemical failure-free survival (bFFS); cancer specific survival (CSS); progression free survival (PFS); disease free survival (DFS); metastasis free survival (MFS); distant metastasis free survival (DMFS); overall survival (OS); prostate specific antigen (PSA); androgen deprivation therapy (ADT); hormone therapy (HT); castration resistant prostate cancer (CRPC); lymph nodes (LN); follow up (FU); quality of life (QOL)

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